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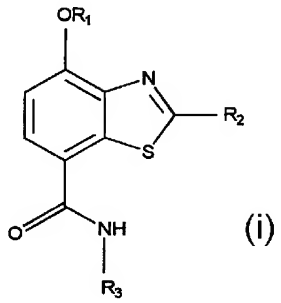
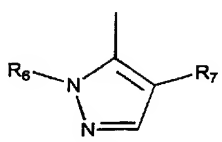
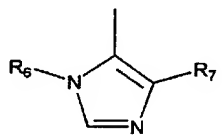
(54) Title: BENZTHIAZOLES AS TNF AND PDE-IV INHIBITORS



(i)



(A)



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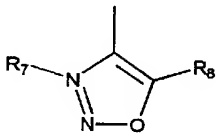

(C)

(57) Abstract: Compounds that are inhibitors of phosphodiesterase and have therapeutic utility, are of formula (i) wherein R_1 is C_{3-6} cycloalkyl, or C_{1-3} alkyl optionally substituted with one or more fluorine atoms; R_2 is C_{1-6} alkyl, C_{3-6} cycloalkyl, CF_3, CH_2CF_3, C_2F_5 or NR_4R_5; R_3 is pyrazole, imidazole or isoxazole group of partial formula (A), (B) or (C) NR_4R_5 is a nitrogen-containing heterocyclic ring; R_6 is C_{1-3} alkyl; and R_7 and R_8, which are the same or different, are each H, C_{1-3} alkyl, halogen, CF_3 or CN, provided that both are not H; or a pharmaceutically-acceptable salt thereof.

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BENZTHIAZOLES AS TNF AND PDE-IV INHIBITORS

Field of the Invention

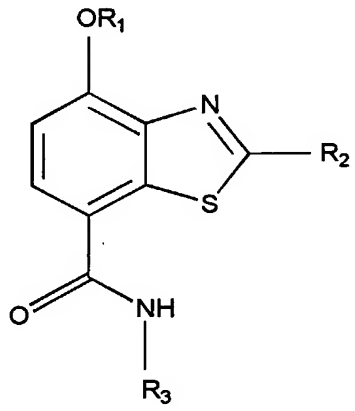
The present invention relates to novel heterocyclic compounds and to their formulation and use as pharmaceuticals.

Background of the Invention

The modes of action of phosphodiesterases and also tumour necrosis factors (TNF), and the therapeutic utilities of inhibitors thereof, are described in WO-A-97/44036 and US Patent No. 5804588, the contents of which are incorporated herein by reference. WO-A-98/22460 and US Patent Application Serial No. 09/422,473, filed Nov. 17, 1997, disclose benzothiazoles that also have such activity.

Summary of the invention

This invention provides novel compounds having therapeutic utility, in particular for the treatment of disease states associated with proteins which mediate cellular activity, for example by inhibiting TNF and/or PDE IV. According to the invention, novel compounds are of formula (i):

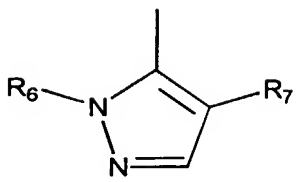


(i)

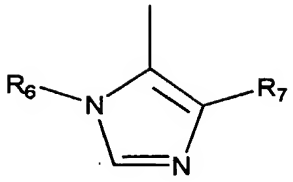
wherein R_1 is C_{3-6}cycloalkyl, or C_{1-3} alkyl optionally substituted with one or more fluorine atoms;

R_2 is C_{1-6} alkyl, C_{3-6} cycloalkyl, CF_3, CH_2CF_3, C_2F_5 or NR_4R_5;

R_3 is a pyrazole, imidazole or isoxazole group of partial formula (A), (B) or (C)



(A)



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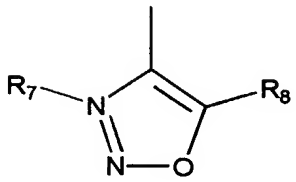


(C)

NR_4R_5 is a nitrogen-containing heterocyclic ring, such as morpholine, pyrrolidine, piperidine, N-methylpiperazine or azetidine;

R_6 is C_{1-3} alkyl; and

R_7 and R_8, which are the same or different, are each H, C_{1-3} alkyl, halogen, CF_3 or CN, provided that both are not H;

or a pharmaceutically-acceptable salt thereof.

In summary, the compounds of the invention represent a selection within the scope of WO-A-98/22460. The novel compounds have superior potency.

This invention provides also a method for mediating or inhibiting the enzymatic activity or catalytic activity of PDE IV in a mammal in need thereof and for inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

Description of the Invention

The term "C_{1-6} alkyl" means a straight or branched chain alkyl moiety having one to six carbon atoms, including, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl and the like. The term "C_{1-3} alkyl" includes, for example, methyl, ethyl, propyl and isopropyl.

The term "C_{3-6} cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopropyl, cyclopentyl and cyclohexyl.

The term "halogen" includes, for example, fluorine, chlorine, bromine and iodine.

In one embodiment of the invention, R_1 is optionally F-substituted alkyl, and R_2 is alkyl, cycloalkyl, CF_3 or NR_4R_5. In a preferred group of compounds of formula (i), R_1 is CH_3 or CHF_2. In the same or another preferred group of compounds of formula (i), R_2 is CF_3, ethyl or cyclopropyl.

R_3, in compounds of the invention, may in particular be a pyrazole of partial formula (A) or an isoxazole of partial formula (C). When R_3 is a pyrazole moiety, R_6 is especially CH_3 and R_7 is particularly CN, CH_3 or CF_3. Where R_3 is an isoxazole moiety, R_7 is especially CH_3, CF_3 or CN, and R_8 is particularly CH_3, CF_3 or CN.

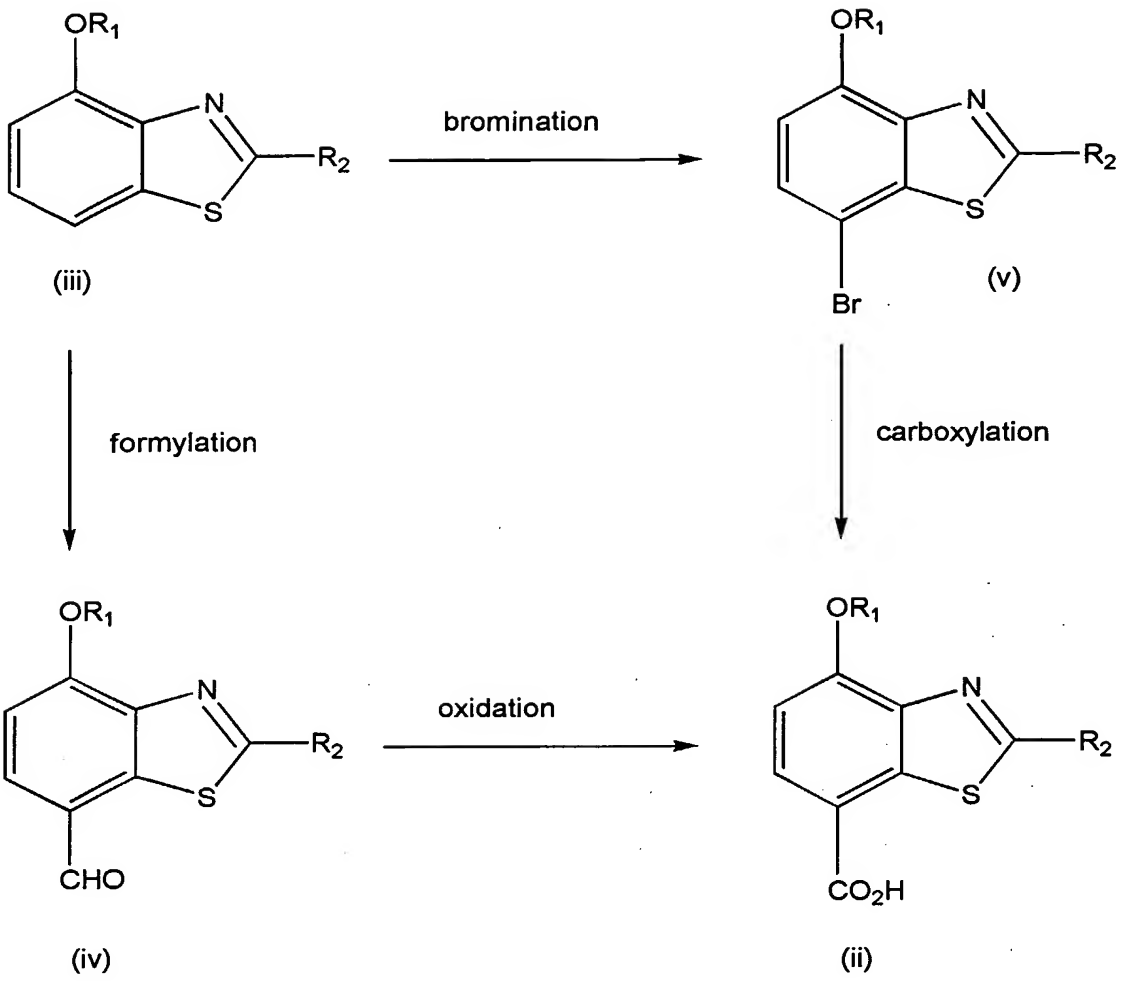
Particularly useful compounds of the invention are those of Examples 1 to 15, below. Especially useful compounds include:

4-methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazole-3-yl)amide and

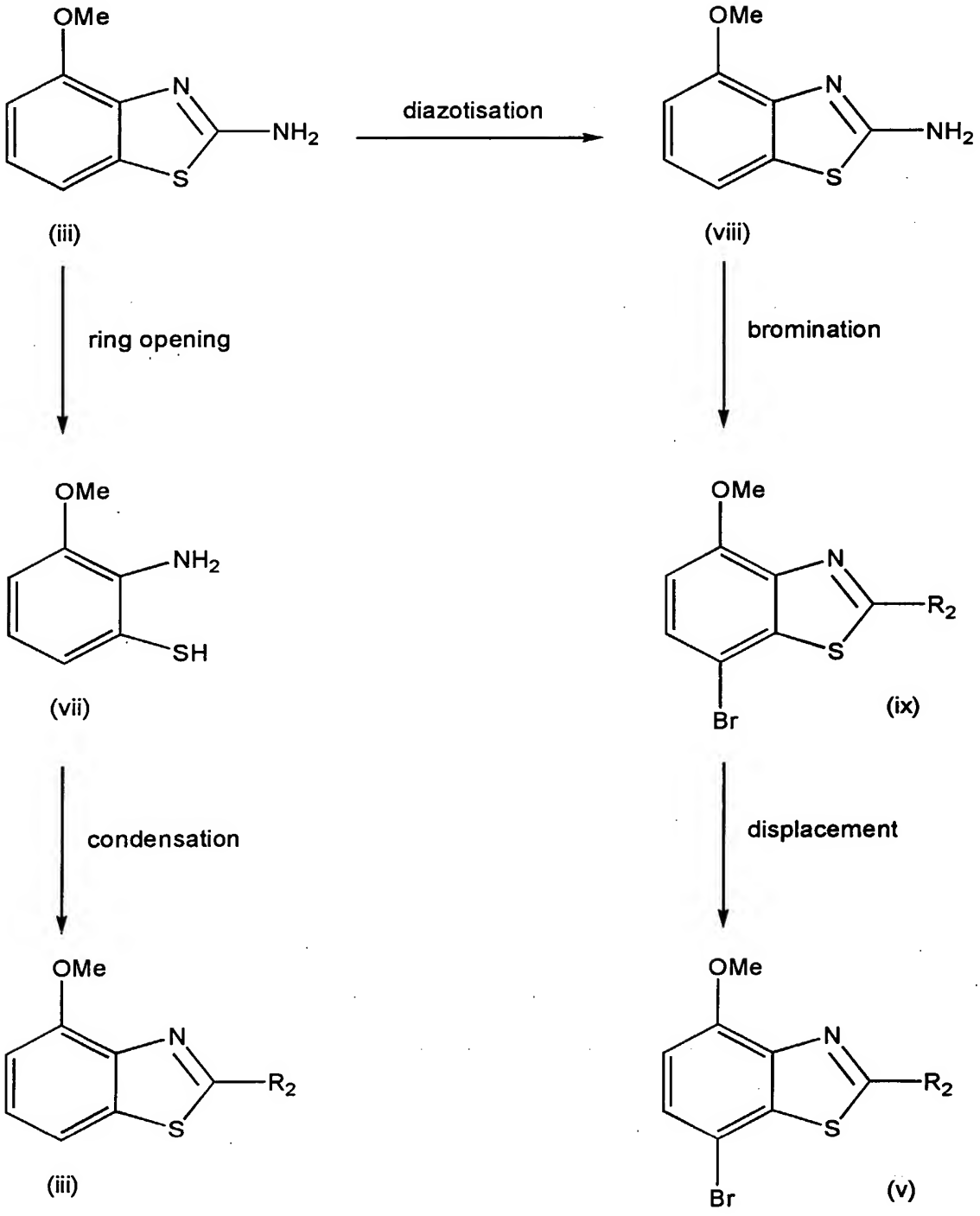
2-cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazole-3-yl)amide.

Certain of the compounds of formula (i) which contain a basic group form acid addition salts. Suitable acid addition salts include pharmaceutically-acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide, and pharmaceutically-acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methanesulphate, α-ketoglutarate, α-glycerophosphate and glucose-1-phosphate. The pharmaceutically-acceptable salts of the compounds of formula (i) are prepared using conventional procedures.

Compounds of the invention may be prepared by reaction of an appropiate carboxylic acid of formula (ii) with a suitable amine R_3NH_2 as described in WO-A-98/22460. Carboxylic acids of formula (ii) are prepared from a compound of formula (iii) using standard conditions known to those skilled in the art, either by formylation to provide an aldehyde of formula (iv) followed by an oxidation to provide an acid of formula (ii), or by bromination to provide bromide of formula (v) followed by carboxylation to provide an acid of formula (ii). Examples of these methods are described in WO-A-98/22460. Amines R_3NH_2 may be commercially available, previously described compounds, or are prepared using standard conditions known to those skilled in the art.



Compounds of formula (iii) or (v) may be prepared from amine (vi) in one of two general methods known to those skilled in the art. Compounds of formula (iii) in which R_2 represents alkyl, cycloalkyl or CF_3 may be prepared as follows. Amine (vi) may be subjected to ring-opening to provide amino-thiol (vii), which may be condensed with anappropiate carboxylic acid or triethylorthopropionate to provide compounds of formula (iii). Alternatively, compounds of formula (v) in which R_2 represents NR_4R_5 may be prepared from amine (vi) by diazotisation/bromination to give bromide (viii), followed by bromination to give dibromide (ix). Subsequent treatment with an appropiate nitrogen-containing aliphatic heterocycle, such as morpholine, provides compounds of formula (v).



For example, benzthiazole (vi) can be ring-opened using any standard conditions known to those skilled in the art, for example by refluxing in sodium hydroxide solution. Treatment of the resulting compound with an appropriate carboxylic acid using any

suitable conditions known to those skilled in the art provides a compound of formula (iii). Suitable conditions include the use of trimethylsilylpolyphosphate in 1,2-dichlorobenzene. To prepare a compound of formula (v), standard conditions are utilised. Thus diazotisation/bromination may be effected using any appropriate conditions, for example by using potassium bromide and sodium nitrite in sulphuric acid. Bromination may be achieved using, for example *N*-bromosuccinimde in acetonitrile. Displacement of the 2-bromo substituent may be carried out by treating dibromide (ix) with the appropiate cyclic amine. Elevated temperatures may favourably be employed for this reaction.

The invention includes the prevention and treatment of TNF-mediated disease or disease states, by which is meant any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance, is a major component, and whose production or action is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-β (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biological responses and binds to the same cellular receptor, both TNF-α and TNF-β are inhibited by compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise.

PDE IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases, including: asthma, chronic bronchitis, atopic dermatitis, atopic eczema, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, psoriasis, Bechet's disease, erythematosis, anaphylactoid purpura nephritis, joint inflammation, arthritis, rheumatoid arthritis and other arthritic conditions such as rheumatoid spondylitis and osteoarthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and conditions associated with cerebral metabolic inhibition, such as cerebral senility, senile dementia (Alzheimer's disease), memory impairment associated with Parkinson's disease, depression and multi-infarct dementia. PDE IV inhibitors are also useful in conditions ameliorated by neuroprotectant activity, such as cardiac arrest, stroke

and intermittent claudication. Additionally, PDE IV inhibitors could have utility as gastroprotectants. A special embodiment of the therapeutic methods of the present invention is the treatment of asthma.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (i). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (i) or a pharmaceutically-acceptable salt thereof.

The compounds of this invention may be also be used in association with the veterinary treatment of animals, other than humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anaemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating parasite, yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis.

The compounds of formula (i) are preferably in pharmaceutically-acceptable form. By pharmaceutically-acceptable form is meant, *inter alia*, a pharmaceutically-acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels. A pharmaceutically-acceptable level of purity will generally be at least 50% excluding normal pharmaceutical additives, preferably 75%, more preferably 90% and still more preferably 95%. When used herein the term "pharmaceutically-acceptable" encompasses materials suitable for both human and veterinary use.

A compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically-acceptable carrier.

Accordingly, the present invention provides a pharmaceutical composition comprising a compound of formula (i) or where appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, and a pharmaceutically-acceptable carrier.

The active compound may be formulated for administration by any suitable route, the preferred route depending upon the disorder for which treatment is required, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral administration or through the respiratory tract. Preparations may be designed to give slow release of the active ingredient.

The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, etc, the compounds of the invention are effective in the treatment of humans.

The compositions of the invention may be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, suppositories, reconstitutable powders, or liquid preparations such as oral or sterile parenteral solutions or suspensions. Topical formulations are also envisaged where appropriate.

In order to obtain consistency of administration it is preferred that a composition of the invention is in the form of a unit dose. Unit dose presentation forms for oral administration may be tablets and capsules and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers for example microcrystalline cellulose, lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically-acceptable wetting agents such as sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers.

Such operations are of course conventional in the art. The tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating.

Oral liquid preparations may be in the form of, for example, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia, non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

Compositions may also suitably be presented for administration to the respiratory tract as a snuff or an aerosol or solution for a nebuliser, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case the particles of active compound suitably have diameters of less than 50 μm, such as from 0.1 to 50 μm, preferably less than 10 μm, for example from 1 to 10 μm, 1 to 5 μm or from 2 to 5 μm. Where appropriate, small amounts of other anti-asthmatics and bronchodilators for example sympathomimetic amines such as isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine; corticosteroids such as prednisolone and adrenal stimulants such as ACTH may be included.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, and, depending on the concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved in water for injection and filter-sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, adjuvants such as a local anaesthetic, a preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be

frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% to 99% by weight, preferably from 10-60% by weight, of the active material, depending on the method of administration.

Compounds of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof and/or a pharmaceutically-acceptable solvate thereof, may also be administered as a topical formulation in combination with conventional topical excipients.

Topical formulations may be presented as, for instance, ointments, creams or lotions, impregnated dressings, gels, gel sticks, spray and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams. The formulations may contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions.

Suitable cream, lotion, gel, stick, ointment, spray or aerosol formulations that may be used for compounds of formula (i) or if appropriate a pharmaceutically-acceptable salt thereof, are conventional formulations well known in the art, for example, as described in standard text books such as Harry's Cosmeticology published by Leonard Hill Books, Remington's Pharmaceutical Sciences, and the British and US Pharmacopoeias.

Suitably, the compound of formula (i), or if appropriate a pharmaceutically-acceptable salt thereof, will compromise from about 0.5 to 20% by weight of the formulation, favourably from about 1 to 10%, for example 2 to 5%.

The dose of the compound used in the treatment of the invention will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and the relative efficacy of the compound. However, as a general guide suitable unit doses may be 0.1 to 1000 mg, such as 0.5 to 200, 0.5 to 100 or 0.5 to 10 mg, for example 0.5, 1, 2, 3, 4 or 5 mg; and such unit doses may be administered more than once a day, for example 2, 3, 4, 5 or 6 times a day, but preferably 1 or 2 times per day, so that the total daily dosage for a 70 kg adult is in the range of about 0.1 to 1000 mg, that is in the range of about 0.001

to 20 mg/kg/day, such as 0.007 to 3, 0.007 to 1.4, 0.007 to 0.14 or 0.01 to 0.5 mg/kg/day, for example 0.01, 0.02, 0.04, 0.05, 0.06, 0.08, 0.1 or 0.2 mg/kg/day, and such therapy may extend for a number of weeks or months.

Assay Methods

The assays used to confirm the phosphodiesterase IV inhibitory activity of compounds of formula (I) are standard assay procedures as disclosed by Schilling *et al*, Anal. Biochem. 216:154 (1994), Thompson and Strada, Adv. Cycl. Nucl. Res. 8:119 (1979) and Gristwood and Owen, Br. J. Pharmacol. 87:91P (1986).

Compounds of formula (i) have exhibited activity at levels consistent with those believed to be useful in treating phosphodiesterase IV related disease states in those assays.

The ability of compounds of formula (i) to inhibit TNF production in human peripheral blood mononuclear cells (PMBC's) is measured as follows. PMBC's are prepared from freshly taken blood or "Buffy coats" by standard procedures. Cells are plated out in RPMI1640 +1% foetal calf serum in the presence and absence of inhibitors. LPS (Lipopolysaccharide (endotoxin); 100 ng/ml) is added and cultures are incubated for 22 h at 37°C in an atmosphere of 95% air/5% CO_2. Supernatants are tested for TNFα by ELISA (Enzyme linked immunosorbent assay) using commercially available kits.

Activity in a guinea pig lung model is measured using the procedures described by Mauser *et al*, Am. Rev. Respir. Dis. 148:1623 (1993), and Am. J. Respir. Crit. Care Med. 152:467 (1995).

Example 6 of WO-A-98/22460 has an IC_{50} 0.39 μM, whereas Example 5 herein (representative of the present invention) has IC_{50} 0.017 μM.

The following Examples illustrate the invention.

Intermediate 1 2-Cyclopropyl-4-methoxybenzothiazole

2-Amino-4-methoxybenzothiazole (1.5g) was heated at reflux for 20hrs in 60% sodium hydroxide solution (100ml). On cooling the reaction was poured into ice, acidified to pH 5 with 1M hydrochloric acid solution and extracted with toluene (3 x 150ml). The combined organic extracts were washed with water (200ml), dried over magnesium sulphate (15g) and the solvent removed *in vacuo* to yield a green oil. This was combined with cyclopropane carboxylic acid (0.58ml), 1,2-dichlorobenzene (30ml) and trimethylsilylpolyphosphate (3ml) and heated at reflux for 90 minutes. On cooling, water

(15ml) was added, the reaction basified to pH 8 using 2M sodium hydroxide solution, and extracted with dichloromethane (3 x 70 ml). The combined organic extracts were dried over magnesium sulphate (10g) and the solvent removed *in vacuo* to yield a brown oil. This was purified by flash chromatography (eluent 50% ethyl acetate/heptane) to yield the title compound as a light brown oil (0.46g).

TLC R_f 0.30 (30% ethyl acetate in hexane)

The following compound was prepared in a similar manner.

Intermediate 2 4-Methoxy-2-trifluoromethylbenzothiazole

Starting from 2-amino-4-methoxybenzothiazole (1.5g) and trifluoroacetic acid (5.5ml), without 1,2 dichlorobenzene. Purification by flash chromatography (eluent 20% ethyl acetate/hexane) yielded the title compound as a light brown oil (0.74g).

TLC R_f 0.70 (50% ethyl acetate in hexane)

Intermediate 3 2-Ethyl-4-methoxybenzothiazole

2-Amino-4-methoxybenzothiazole (4g) was heated at reflux for 20hrs in 60% sodium hydroxide solution (250ml). On cooling the reaction was poured into ice, acidified to pH 5 with 1M hydrochloric acid solution and extracted with toluene (3 x 200ml). The combined organic extracts were washed with water (300ml), dried over magnesium sulphate (20g) and the solvent removed *in vacuo* to yield a green oil. This was combined with triethylorthopropionate (19.5ml) and heated at 140°C for 20 hrs. On cooling, water (100ml) was added and the reaction extracted with ethyl acetate (2 x 50ml). The combined organic extracts were dried over magnesium sulphate (10g) and the solvent removed *in vacuo* to yield a brown oil. This was purified by flash chromatography (eluent 10–20% ethyl acetate/hexane to yield the title compound as a light brown oil (0.46g).

TLC R_f 0.18 (20% ethyl acetate in hexane)

Intermediate 4 2-Bromo-4-methoxybenzothiazole

To a solution of 2-amino-4-methoxybenzothiazole (1.5g) and potassium bromide (3.5g) in sulphuric acid (1.25M, 50ml) at 0°C was added sodium nitrite (0.86g) over a period of 1hr. The reaction was allowed to warm to room temperature and stirred for 2hrs, before being extracted with dichloromethane (3 x 50ml). The combined organic extracts were dried over magnesium sulphate (5g), and the solvent removed *in vacuo* to yield an off white solid. This was purified by flash chromatography (eluent 50% ethyl acetate/hexane) to yield the title compound as a white solid (1.6g).

TLC R_f 0.30 (20% ethyl acetate in hexane)

Intermediate 5 7-Bromo-2-ethyl-4-methoxybenzothiazole

To a stirred solution of 2-ethyl-4-methoxybenzothiazole (2.5g) in acetonitrile (50ml) was added *N*-bromosuccinamide (2.3g). The reaction was stirred at room temperature for 20 hrs, before the acetonitrile was removed *in vacuo*, and the resulting residue purified by flash chromatography (eluent ethyl acetate) to yield the title compound as an off-white solid (2.9g).

TLC R_f 0.60 (50% ethyl acetate in hexane)

The following compounds were prepared in a similar manner.

Intermediate 6 7-Bromo-2-cyclopropyl-4-methoxybenzothiazole

Starting from 2-cyclopropyl-4-methoxybenzothiazole (0.3g), *N*-bromosuccinamide (0.17g) and acetonitrile (30ml). Purification by flash chromatography (eluent 30% ethyl acetate/heptane) yielded the title compound as an off-white solid (0.24g).

TLC R_f 0.30 (30% ethyl acetate in heptane)

Intermediate 7 2,7-Dibromo-4-methoxybenzothiazole

Starting from 2-bromo-4-methoxybenzothiazole (1.6g), *N*-bromosuccinamide (0.91g) and acetonitrile (100ml). Purification by flash chromatography (eluent 20% ethylacetate/hexane) yielded the title compound as an off-white solid (1.8g).

TLC R_f 0.31 (20% ethyl acetate in heptane).

Intermediate 8 7-Bromo-4-methoxy-2-(morpholin-4-yl)benzothiazole

A suspension of 2,7-dibromo-4-methoxybenzothiazole (1.8g) and morpholine (10ml) in tetrahydrofuran (10ml) was heated at 80°C for 2 hours. The solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (100ml) and water (100ml). The organic layer was dried over magnesium sulphate (3g), filtered and the filtrate evaporated *in vacuo* to yield an off white solid. This was purified by recrystallisation from ethyl acetate/hexane to yield the title compound as a white solid (1.2g).

TLC R_f 0.39 (50% ethyl acetate in hexane).

The following compounds were prepared in a similar manner.

Intermediate 9 7-Bromo-4-methoxy-2-(piperidin-1-yl)benzothiazole

Starting from 2,7-dibromo-4-methoxybenzothiazole (1.5g), piperidine (0.8g) and tetrahydrofuran (20ml). Purification by flash chromatography (eluent 50% ethylacetate/hexane) yielded the title compound as an off-white solid (1.5g).

TLC R_f 0.67 (ethyl acetate)

Intermediate 10 7-Bromo-2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole

Starting from 2,7-dibromo-4-methoxybenzothiazole (1.25g), *t*-butyl-1-piperazine (1.6g) and tetrahydrofuran (40ml). Purification by flash chromatography (eluent 40-60% ethyl acetate/hexane) yielded the title compound as a pale yellow solid (1.5g). TLC R_f 0.49 (50 % ethyl acetate in hexane)

Intermediate 11 2-Ethyl-4-methoxybenzothiazole-7-carboxylic acid

A mixture of 7-bromo-2-ethyl-4-methoxybenzothiazole (2.96g), palladium (II) acetate (240mg), *bis*-diphenylphosphinopropane (900mg), and triethylamine (15ml) in tetrahydrofuran (150ml) and water (20ml) was charged with 150psi of carbon monoxide and stirred at 90°C for 3 days. The organic solvent was removed *in vacuo* and the residue partitioned between ethyl acetate (50ml) and aqueous sodium hydroxide (1M, 2 x 50ml). The aqueous extracts were combined, acidified to pH 4 with glacial acetic acid, extracted with ethyl acetate (3 x 50ml). The organic extracts were combined, dried over magnesium sulphate (5g), filtered, and the filtrate evaporated *in vacuo*. Recrystallisation from ethyl acetate/hexane gave the desired product as an off-white solid (2.2g).

TLC R_f 0.30 (50%ethyl acetate in hexane)

The following compounds were prepared in a similar manner.

Intermediate 12 2-Cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid

Starting from 7-bromo-2-cyclopropyl-4-methoxybenzothiazole (515mg), palladium (II) acetate (40mg), *bis*-diphenylphosphinopropane (149mg), and triethylamine (2.5 ml) in tetrahydrofuran (15ml) and water (7 ml). Trituration of the residue with diethyl ether yielded the title compound as an off-white solid (360mg).

TLC R_f 0.49 (ethyl acetate)

Intermediate 13 2-(Morpholin-4-yl)-4-methoxybenzothiazole-7-carboxylic acid

Starting from 7-bromo-2-(morpholin-4-yl)-4-methoxybenzothiazole (600mg), palladium (II) acetate (41mg), *bis*-diphenylphosphinopropane (150mg), and triethylamine

(2.5 ml) in tetrahydrofuran (100ml) and water (10 ml). Recrystallisation fron ethyl acetate/hexane yielded the title compound as an off-white solid (395mg).

TLC R_f 0.12 (50% ethyl acetate in hexane)

Intermediate 14 2-(Piperidin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid

Starting from 7-bromo-2-(piperidin-1-yl)-4-methoxybenzothiazole (1.4g), palladium (II) acetate (100mg), *bis*-diphenylphosphinopropane (350mg), and triethylamine (6ml) in tetrahydrofuran (200ml) and water (20ml). Trituration of the residue with diethyl ether yielded the title compound as a yellow solid (700mg).

TLC R_f 0.66 (ethyl acetate)

Intermediate 15 2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid

Starting from 7-bromo-2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole (1.5g), palladium (II) acetate (85mg), *bis*-diphenylphosphinopropane (310mg), and triethylamine (5.3ml) in tetrahydrofuran (60ml) and water (30ml). Purification by column chromatography (eluent 20% ethyl acetate in heptane) yielded the title compound as an off-white solid (290mg).

TLC R_f 0.16 (50% ethyl acetate in hexane).

Intermediate 16 4-Methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid

4-Methoxy-2-trifluoromethylbenzothiazole (1.5g) was dissolved in dichloromethane (30ml) and cooled to 0°C and treated with titanium tetrachloride (1.0M solution in dichloromethane, 13.8ml). Dichloromethyl methyl ether (0.62ml) was then added dropwise and the reaction stirred at 0°C for 30 minutes, room temperature for 1 hr and reflux for 1 hr. On cooling the reaction was poured into ice and the reaction extracted with dichloromethane (2 x 100ml). The combined organic extracts were dried over magnesium sulphate (5g) and the solvent removed *in vacuo* to yield a brown oil. This was dissolved in *tert*-butanol (40ml) and 2-methyl-2-butene (3.5ml) was added. Sodium phosphate (4.7g) and sodium chlorite (3.2g) were then added and the reaction stirred at room temperature for 16 hrs. Water (10ml) was added and the solvent was removed *in vacuo*, and the residue basified to pH8 with potassium hydroxide. The aqueous was extracted with dichloromethane (3 x 30ml), before being acidified with 1M hydrochloric acid to pH6, and extracted with ethyl acetate (3 x 30ml). The combined ethyl acetate

extracts were dried over magnesium sulphate (5g) and the solvent removed in *vacuo* to yield the title compound as a white solid (0.14g).

TLC R_f 0.55 (50% ethyl acetate in hexane)

Intermediate 17 4-Methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid 4-nitrophenyl ester

A suspension of 4-methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid (140mg) in dichloromethane (10ml) was treated with *p*-nitrophenol (72mg), dimethylaminopyridine (catalytic) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (150mg). The mixture was stirred at room temperature for 12 hours and the reaction washed with water (10 ml). The organic layer was separated, dried over magnesium sulphate (5g) and evaporated *in vacuo*. Purification by flash chromatography (eluent 50% ethyl acetate/hexane) yielded the title compound as an off-white solid (150mg).

TLC R_f 0.13 (50% ethyl acetate in heptane)

The following compounds were prepared in a similar manner.

Intermediate 18 2-Cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid 4-nitrophenyl ester

Starting from 2-cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (270mg), *p*-nitrophenol (165mg), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (228mg) in dichloromethane (35ml). Trituration of the residue with diethyl ether yielded the title compound as a bright yellow solid (290mg).

TLC R_f 0.60 (ethyl acetate)

Intermediate 19 2-(Piperidin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid 4-nitrophenyl ester

Starting from 2-(piperidin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (190mg), *p*-nitrophenol (100mg), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (150mg) in dichloromethane (20ml). Purification by column chromatography (eluent 50% ethylacetate in hexane) yielded the title compound as an off-white solid (240mg).

TLC R_f 0.39 (50% ethyl acetate in hexane)

Intermediate 20 **2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid 4-nitrophenyl ester**

Starting from 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (500 mg), *p*-nitrophenol (190mg), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (370mg) in dichloromethane (30ml). Purification by column chromatography (eluent ethyl acetate) yielded the title compound as an off-white solid (460mg).

TLC R_f 0.28 (50% ethyl acetate in hexane)

Example 1 **2-Ethyl-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide**

To a suspension of 2-ethyl-4-methoxybenzothiazole-7-carboxylic acid (0.1g) in dichloromethane (10ml) was added oxalyl chloride (0.08ml) and dimethylformamide (1 drop). The reaction was stirred at room temperature for 16 hrs, and then the solvent was removed *in vacuo* to yield a brown solid residue. This was taken up in dichloromethane (30ml) and 3,5-dimethylisoxazol-4-amine (0.05g) was added followed by triethylamine (0.15ml) and the reaction stirred at room temperature for 16 hrs. The solvent was removed *in* vacuo and the product purified by flash chromatography (eluent ethyl acetate) to yield the title compound as an off-white solid (0.016g).

TLC R_f 0.38 (ethyl acetate); Mpt 85 – 87°C

The following compounds were prepared in a similar manner.

Example 2 **4-Methoxy-2-(morpholin-4-yl)benzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide**

Starting from 4-methoxy-2-(morpholin-4-yl)benzothiazole-7-carboxylic acid (0.13g), oxalyl chloride (2.0ml), dichloromethane (10ml) and dimethylformamide (1 drop), followed by 3,5-dimethylisoxazol-4-amine (0.05g), triethylamine (0.1ml) and dichloromethane (10ml). Purification by flash chromatography (eluent 50% ethyl acetate/hexane – ethyl acetate) yielded the title compound as an off-white solid (0.066g).

TLC R_f 0.40 (ethyl acetate); Mpt 326 -327°C

Example 3 **2-Cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide**

Starting from 2-cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (0.20g), oxalyl chloride (0.11ml), dichloromethane (30ml) and dimethylformamide (1 drop),

followed by 3,5-dimethylisoxazol-4-amine (0.20g), triethylamine (0.22ml) and dichloromethane (30ml). Purification by flash chromatography (eluent 50% ethyl acetate/heptane) yielded the title compound as a white solid (0.067g).

TLC R_f 0.33 (ethyl acetate); Mpt 196 - 197°C

Example 4 **4-Methoxy-2-(piperidin-1-yl)-benzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide**

Starting from 4-methoxy-2-(piperidin-1-yl)benzothiazole-7-carboxylic acid (0.24g), oxalyl chloride (2.0 ml), dichloromethane (20ml) and dimethylformamide (1 drop), followed by 3,5-dimethylisoxazol-4-amine (0.10g), triethylamine (0.25ml) and dichloromethane (20ml). Purification by flash chromatography (eluent 5% methanol in dichloromethane) yielded the title compound as a white solid (29mg).

TLC R_f 0.49 (ethyl acetate); MS found M+1 387.

Example 5 **2-Ethyl-4-methoxybenzothiazole-7-carboxylic acid (2-methyl-2H-pyrazol-3-yl)amide**

Starting from 2-ethyl-4-methoxybenzothiazole-7-carboxylic acid (0.2g), oxalyl chloride (0.15ml), dichloromethane (20ml) and dimethylformamide (1 drop), followed by 2-methyl-2H-pyrazol-3-ylamine (0.17g), triethylamine (0.24ml) and dichloromethane (40ml). Purification by flash chromatography (eluent 10% methanol/dichloromethane) yielded the title compound as a yellow solid (0.08g).

TLC R_f 0.52 (10% methanol in dichloromethane); Mpt 185 - 186°C.

Example 6 **2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide**

Starting from 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (0.11g), oxalyl chloride (0.06ml), dichloromethane (10ml) and dimethylformamide (1 drop), followed by 3,5-dimethylisoxazol-4-amine (70 mg), triethylamine (0.08ml) and dichloromethane (10ml). Purification by flash chromatography (eluent 75% ethyl acetate in hexane) yielded the title compound as a yellow solid (29 mg).

TLC R_f 0.51 (ethyl acetate); Mpt 231-233°C.

Example 7 **2-Ethyl-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

To a suspension of 2-ethyl-4-methoxybenzothiazole-7-carboxylic acid (0.1g) in dichloromethane (10ml) was added oxalyl chloride (1.0ml) and dimethylformamide (1 drop). The reaction was stirred at room temperature for 16 hrs, and then the solvent was removed *in vacuo* to yield a brown solid residue. 5-Amino-1-methyl-1H-pyrazole-4-carbonitrile (0.1g) was taken up in dichloromethane (10ml) and sodium hexamethyldisilylamine (1.0M in tetrahydrofuran, 0.84ml) was added. After 5 minutes the acid chloride was added and the reaction stirred at room temperature for 16 hrs. The solvent was removed *in vacuo* and the product purified by flash chromatography (eluent 50% ethyl acetate/hexane – 75% ethyl acetate/hexane) to yield the title compound as an off-white solid (0.088g).

TLC R_f 0.13 (50% ethyl acetate/hexane); Mpt 190 – 191°C

The following compound was prepared in a similar manner.

Example 8 **4-Methoxy-2-(morpholin-4-yl)-benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

Starting with 4-methoxy-2-(morpholin-4-yl)benzothiazole-7-carboxylic acid (0.13g) oxalyl chloride (0.10ml), dichloromethane (10ml) and dimethylformamide (1 drop), followed by 5-amino-1-methyl-1H-pyrazole-4-carbonitrile (0.11g), sodium hexamethyldisilylamine (1.0M in tetrahydrofuran, 0.88ml) and dichloromethane (10ml). Purification by flash chromatography (eluent ethyl acetate) yielded the title compound as an off-white solid (0.02g).

TLC R_f 0.45 (ethyl acetate); Mpt 299 – 300°C

Example 9 **4-Methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

A solution of 5-amino-1-methyl-1H-pyrazole-4-carbonitrile (93mg) in dimethyl formamide (10ml) was treated with a solution of sodium hexamethyldisilazide in tetrahydrofuran (0.76ml, 1.0M). After three minutes the mixture was treated with 4-methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid 4-nitrophenyl ester (150 mg) and the reaction stirred at room temperature for 2 hours. The solvent was removed *in vacuo*. Purification by flash chromatography (eluent ethyl acetate) to yield the title compound as an off-white solid (50 mg).

TLC R_f 0.48 (ethyl acetate); MS found M+1 382.

The following compounds were prepared in a similar manner.

Example 10 **2-Cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

Starting from 5-amino-1-methyl-1H-pyrazole-4-carbonitrile (90mg) in dimethyl formamide (30ml), sodium hexamethyldisilazide in tetrahydrofuran (1.08ml, 1.0 M), and 2-cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid 4-nitrophenyl ester (200 mg). Purification by flash chromatography (eluent 10% methanol in dichloromethane) to yield the title compound as an off-white solid (95 mg).

TLC R_f 0.30 (10% methanol in dichloromethane); Mpt 259 – 260°C.

Example 11 **4-Methoxy-2-(piperidin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

Starting from 5-amino-1-methyl-1H-pyrazole-4-carbonitrile (125 mg) in dimethyl formamide (10ml), sodium hexamethyldisilazide in tetrahydrofuran (1.1ml, 1.0 M), and 4-methoxy-2-(piperidin-1-yl)benzothiazole-7-carboxylic acid 4-nitrophenyl ester (210 mg). Purification by flash chromatography (eluent 5% methanol in dichloromethane) followed by trituration with ethyl acetate yielded the title compound as an off-white solid (152 mg).

TLC R_f 0.48 (ethyl acetate); Mpt 290-291°C.

Example 12 **2-(4-*tert*-Butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

Starting from 5-amino-1-methyl-1H-pyrazole-4-carbonitrile (119mg) in dimethyl formamide (10ml), sodium hexamethyldisilazide in tetrahydrofuran (0.97ml, 1.0 M), 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid 4-nitrophenyl ester (250 mg). Purification by flash chromatography (eluent 5% methanol in dichloromethane) followed by trituration with diethyl ether yielded the title compound as a pale yellow solid (260mg).

TLC R_f 0.48 (ethyl acetate); Mpt 231-232°C.

Example 13 **4-Methoxy-2-(piperazin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide, trifluoroacetic acid salt**

A solution of 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide (260mg) and dicloromethane (10ml) was treated with trifluoroacetic acid and the mixture stirred at room temperature for one hour. The solvent was removed *in vacuo* and the residue triturated with diethyl ether to yield the title compound as a yellow solid (285mg).

TLC R_f 0.09 (10% methanol in dichloromethane); Mpt 242-244°C.

The following compounds were prepared in a similar manner.

Example 14 **4-Methoxy-2-(piperazin-1-yl)benzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide, trifluoroacetic acid salt**

Starting from 2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide (0.24g), trifluoroacetic acid (2.0 ml), and dichloromethane (20ml). Trituration with diethyl ether yielded the title compound as a white solid (2mg).

TLC R_f 0.01 (10% methanol in dichloromethane).

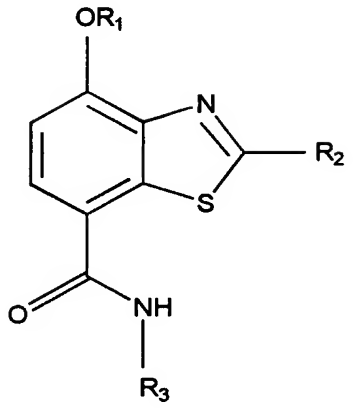
Example 15 **4-Methoxy-2-(4-methylpiperazin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide**

A suspension of 4-methoxy-2-(piperazin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide trifluoroacetic acid salt (275mg) in acetonitrile (20ml) was treated with formaldehyde (0.44 ml, 37% aqueous solution), sodium cyanoborohydride (102mg), and acetic acid (0.3ml) and the mixture stirred at room temperature of 12 hours. The solvent was evaporated *in vacuo* and the residue partitioned between aqueous sodium hydroxide (10ml, 1M) and dichloromethane (100ml). The aqueous layer was separated, was neutralised with acetic acid, and extracted with 2% methanol in dichloromethane (2 x 75ml). The extracts were combined, dried over magnesium sulphate (5g), filtered, and the filtrate evaporated *in vacuo*. Purification by column chromatography (eluent 5% methanol in dichloromethane) followed by trituration with diethyl ether yielded the title compound as a pale yellow solid (40mg).

TLC R_f 0.14 (10% methanol in dichloromethane); Mpt 249-251°C.

CLAIMS

1. A compound of the formula

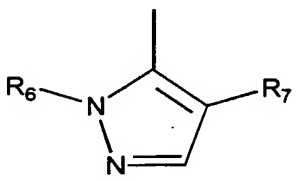


(I)

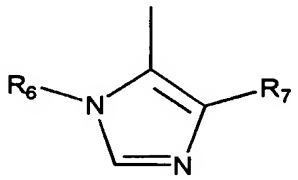
wherein R_1 is C_{3-6} cycloalkyl, or C_{1-3} alkyl optionally substituted with one or more fluorine atoms;

R_2 is C_{1-6} alkyl, C_{3-6} cycloalkyl, CF_3, CH_2CF_3, C_2F_5 or NR_4R_5;

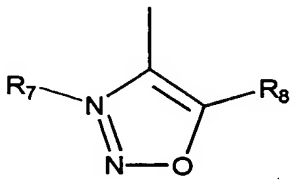
R_3 is a pyrazole, imidazole or isoxazole group of partial formula (A), (B) or (C)



(A)



(B)



(C)

NR_4R_5 is a nitrogen-containing heterocyclic ring;

R_6 is C_{1-3} alkyl; and

R_7 and R_8, which are the same or different, are each H, C_{1-3} alkyl, halogen, CF_3 or CN, provided that both are not H;

or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1, wherein R_3 is a pyrazole or isoxazole group.

3. A compound of claim 2, wherein R_3 is a pyrazole group, R_6 is CH_3 and R_7 is CN, CH_3 or CF_3.

4. A compound of claim 2, wherein R_3 is an isoxazole group and R_7 and R_8 are independently selected from CH_3, CF_3 and CN.

5. A compound of any preceding claim, wherein R_1 is optionally F-substituted alkyl and R_2 is alkyl, cycloalkyl, CF_3 or NR_4R_5.

6. A compound of claim 5, wherien R_1 is CH_3 or CHF_2.

7. A compound of claim 5 or claim 6, wherein R_2 is CF_3, ethyl or cyclopropyl.

8. A compound of claim 1, selected from

2-ethyl-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)-amide,

4-methoxy-2-(morpholin-4-yl)-benzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide,

2-cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide,

4-methoxy-2-(piperidin-1-yl)-benzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide,

2-ethyl-4-methoxybenzothiazole-7-carboxylic acid (2-methyl-2H-pyrazol-3-yl)-amide,

2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide,

2-ethyl-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide

4-methoxy-2-(morpholin-4-yl)-benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)-amide,

4-methoxy-2-(piperidin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide,

2-(4-*tert*-butoxycarbonylpiperazin-1-yl)-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide,

4-methoxy-2-(piperazin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide, trifluoroacetic acid salt,

4-methoxy-2-(piperazin-1-yl)benzothiazole-7-carboxylic acid (3,5-dimethylisoxazol-4-yl)amide, trifluoroacetic acid salt, and

4-methoxy-2-(4-methylpiperazin-1-yl)benzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide.

9. A compound of claim 1, selected from

4-methoxy-2-trifluoromethylbenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide and

2-cyclopropyl-4-methoxybenzothiazole-7-carboxylic acid (4-cyano-2-methyl-2H-pyrazol-3-yl)amide.

10. A composition for use in therapy, comprising a compound of any preceding claim and a pharmaceutically acceptable carrier or diluent.

11. Use of a compound of any of claims 1 to 9, for the manufacture of a medicament for use in the treatment of a disease state that is capable of being modulated by inhibition of phosphodiesterase IV or Tumour Necrosis Factor, or that is a pathological condition associated with a function of phosphodiesterase IV, eosinophil accumulation or a function of the eosinophil.

12. The use of claim 11, wherein the disease state is an inflammatory disease or autoimmune disease.

13. The use of claim 11, wherein the disease state is selected from asthma, chronic bronchitis, chronic pulmonary inflammatory disease, chronic obstructive airways disease, atopic dermatitis, allergic rhinitis, psoriasis, arthritis, rheumatoid arthritis, joint inflammation, ulcerative colitis, Crohn's disease, atopic eczema, stroke, bone resorption disease, multiple sclerosis and inflammatory bowel disease.

14. The use of claim 11, wherein the disease state is selected from urticaria, allergic conjunctivitis, vernal conjunctivitis, inflammation of the eye, allergic responses in the eye, eosinophilic granuloma, gouty arthritis and other arthritic conditions, adult respiratory distress syndrome, diabetes insipidus, keratosis, cerebral senility, multi-infarct dementia, senile dementia, memory impairment associated with Parkinson's disease, depression, cardiac arrest, intermittent claudication, rheumatoid spondylitis, osteoarthritis, sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, acute respiratory distress syndrome, cerebral malaria, silicosis, pulmonary sarcoidosis, reperfusion injury, graft vs host reaction, allograft rejection, infection-related fever or myalgia, malaria, HIV, AIDS, ARC, cachexia, keloid formation, scar tissue formation, pyresis, systemic lupus erythematosus, type 1 diabetes mellitus, Bechet's disease, anaphylactoid purpura nephritis, chronic glomerulonephritis, leukaemia, tarditive

dyskinesia, yeast or fungal infection, conditions requiring gastroprotection, and neurogenic inflammatory disease associated with irritation and pain.

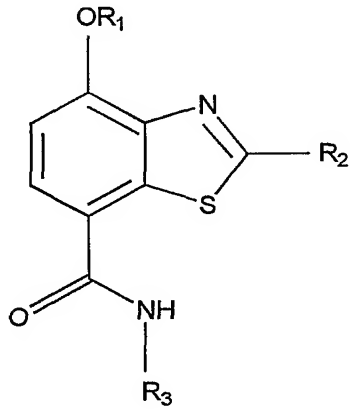
15. The use of claim 11, wherein the disease state is asthma.

16. The use of claim 11, wherein the disease state is chronic obstructive airways disease or chronic bronchitis.

AMENDED CLAIMS

[received by the International Bureau on 21 June 2001 (21.06.01);
original claims 1 amended; remaining claims unchanged (1 page)]

1.(amended) A compound of the formula

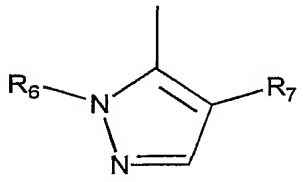


(i)

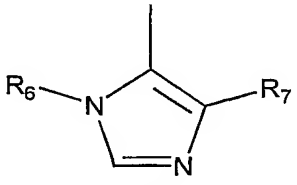
wherein R_1 is C_{3-6} cycloalkyl, or C_{1-3} alkyl optionally substituted with one or more fluorine atoms;

R_2 is C_{1-6} alkyl, C_{3-6} cycloalkyl, CF_3, CH_2CF_3, C_2F_5 or NR_4R_5;

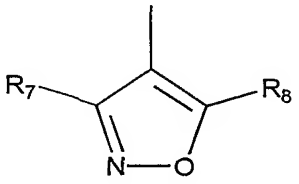
R_3 is a pyrazole, imidazole or isoxazole group of partial formula (A), (B) or (C)



(A)



(B)



(C)

NR_4R_5 is a nitrogen-containing heterocyclic ring;

R_6 is C_{1-3} alkyl; and

R_7 and R_8, which are the same or different, are each H, C_{1-3} alkyl, halogen, CF_3 or CN, provided that both are not H;

or a pharmaceutically-acceptable salt thereof.

2. A compound of claim 1, wherein R_3 is a pyrazole or isoxazole group.

3. A compound of claim 2, wherein R_3 is a pyrazole group, R_6 is CH_3 and R_7 is CN, CH_3 or CF_3.

4. A compound of claim 2, wherein R_3 is an isoxazole group and R_7 and R_8 are independently selected from CH_3, CF_3 and CN.

INTERNATIONAL SEARCH REPORT

Int ›nal Application No
PCT/GB 01/00517

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D417/12 A61K31/425 A61P11/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 22460 A (DARWIN DISCOVERY LTD) 28 May 1998 (1998-05-28) cited in the application claim 1; example 6	1-16
A	WO 99 24035 A (SQUIBB BRISTOL MYERS CO) 20 May 1999 (1999-05-20) claim 1	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 April 2001	24/04/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gettins, M

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/GB 01/00517

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